

Application No. 10/677,116
RCE Submission dated May 6, 2008
Reply to Office Action of April 8, 2008

Docket No.: 60023(50152)

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CLAIMS

Claims 1-7 (Canceled)

8. (currently amended) Compounds of the following as claimed in claim 1,
~~wherein the compounds are:~~

- (1) (3R,4R)-2,2-Dimethyl-7-methoxy-4-(4-(((2R)-3-methylamino-2-hydroxy}propyloxy]phenyl)-3-phenylchroman;
- (2) (3R,4R)-2,2-Dimethyl-7-methoxy-4-(4-(((2R)-3-ethylamino-2-hydroxy}propyloxy]phenyl)-3-phenylchroman;
- (3) (3R,4R)-2,2-Dimethyl-7-methoxy-3-phenyl-4-(4-(((2R)-3-propylamino-2-hydroxy}propyloxy]phenyl)chroman;
- (4) (3R,4R)-4-(4-(((2R)-3-Butylamino-2-hydroxy}propyloxy]phenyl)-2,2-dimethyl-7-methoxy-3-phenylchroman;
- (5) (3R,4R)-2,2-Dimethyl-7-methoxy-4-(4-(((2R)-3-pentylamino-2-hydroxy}propyloxy]phenyl)-3-phenylchroman;
- (6) (3R,4R)-2,2-Dimethyl-4-(4-(((2R)-3-dimethylamino-2-[]hydroxy}propyloxy]phenyl)-7-methoxy-3-phenylchroman;
- (7) (3R,4R)-4-(4-(((2R)-3-Diethylamino-2-hydroxy}propyloxy]phenyl)-2,2-dimethyl-7-methoxy-3-phenylchroman;
- (8) (3R,4R)-2,2-Dimethyl-4-(4-(((2R)-3-dipropylamino-2-[]hydroxy}propyloxy]phenyl)-7-methoxy-3-phenylchroman;
- (9) (3R,4R)-4-(4-(((2R)-3-Dibutylamino-2-hydroxy}propyloxy]phenyl)-2,2-dimethoxy-3-phenylchroman;
- (10) (3R,4R)-2,2-Dimethyl-4-(4-(((2R)-3-dipentylamino-2-hydroxy}propyloxy]phenyl)-7-methoxy-3-phenylchroman;

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- (11) (3R,4R)-2,2-Dimethyl-7-methoxy-3-phenyl-4-(4-[(2R)-3-pyrrolidino-2-hydroxy] propyloxy]phenyl)-chroman;
- (12) (3R,4R)-2,2-Dimethyl-7-methoxy-3-phenyl-4-(4-[(2R)-3-piperidino-2-hydroxy] propyloxy]phenyl)-chroman;
- (13) (3R,4R)-2,2-Dimethyl-7-methoxy-3-phenyl-4-(4-[(2R)-3-morpholino-2-hydroxy] propyloxy]phenyl)-chroman;
- (14) (3R,4R)-2,2-Dimethyl-7-methoxy-3-phenyl-4-(4-[(2R)-3-piperazino-2-hydroxy] propyloxy]phenyl)-chroman;
- (15) (3R,4R)-2,2-Dimethyl-7-methoxy-3-phenyl-4-(4-[(2R)-3-cyclohexylamino-2-hydroxy] propyloxy]phenyl)-chroman;
- (16) (3R,4R)-2,2-Dimethyl-7-methoxy-4-(4-[(2S)-3-methylamino-2-hydroxy] propyloxy]phenyl)-3-phenylchroman;
- (17) (3R,4R)-2,2-Dimethyl-7-methoxy-4-(4-[(2S)-3-ethylamino-2-hydroxy] propyloxy]phenyl)-3-phenylchroman;
- (18) (3R,4R)-2,2-Dimethyl-7-methoxy-3-phenyl-4-(4-[(2S)-3-propylamino-2-hydroxy] propyloxy]phenyl)-chroman;
- (19) (3R,4R)-4-[4-(4-[(2S)-3-Butylamino-2-hydroxy] propyloxy]phenyl)-2,2-dimethyl-7-methoxy-3-phenylchroman;
- (20) (3R,4R)-2,2-Dimethyl-7-methoxy-4-(4-[(2S)-3-pentylamino-2-hydroxy] propyloxy]phenyl)-3-phenylchroman;
- (21) (3R,4R)-2,2-Dimethyl-4-(4-[(2S)-3-dimethylamino-2-[-]hydroxy] propyloxy]phenyl)-7-methoxy-3-phenylchroman;
- (22) (3R,4R)-4-(4-[(2S)-3-Diethylamino-2-hydroxy]propyloxy]phenyl)-2,2-dimethyl-7-methoxy-3-phenylchroman;

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(23) (3R,4R)-2,2-Dimethyl-4-(4-[(2S)-3-dipropylamino-2-hydroxy]propyloxy]phenyl)-7-methoxy-3-phenylchroman;

(24) (3R,4R)-4-((4-[(2S)-3-Dibutylamino-2-hydroxy]propyloxy]phenyl)-3-phenyl)-2,2-dimethoxy-3-phenylchroman;

(25) (3R,4R)-2,2-Dimethyl-4-(4-[(2S)-3-dipentylamino-2-hydroxy]propyloxy]phenyl)-7-methoxy-3-phenylchroman;

(26) (3R,4R)-2,2-Dimethyl-7-methoxy-3-phenyl-4-(4-[(2S)-3-pyrrolidino-2-hydroxy]propyloxy]phenyl)-chroman;

(27) (3R,4R)-2,2-Dimethyl-7-methoxy-3-phenyl-4-(4-[(2S)-3-piperidino-2-hydroxy]propyloxy]phenyl)-chroman;

(28) (3R,4R)-2,2-Dimethyl-7-methoxy-3-phenyl-4-(4-[(2S)-3-morpholino-2-hydroxy]propyloxy]phenyl)-chroman;

(29) (3R,4R)-2,2-Dimethyl-7-methoxy-3-phenyl-4-(4-[(2S)-3-piperazino-2-hydroxy]propyloxy]phenyl)-chroman; and

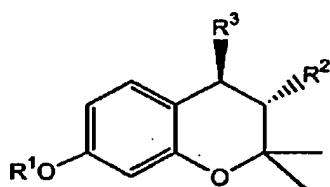
(30) (3R,4R)-2,2-Dimethyl-7-methoxy-3-phenyl-4-(4-[(2S)-3-cyclohexylamino-2-hydroxy]propyloxy]phenyl)-chroman.

Claims 9-12 (Canceled)

Claim 13 (Currently amended) A process for the preparation of compounds of formula I,

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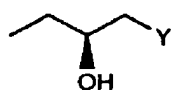
(I)

wherein:

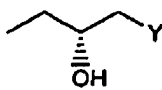
R¹ is H or C1-C6 alkyl; C3-C7 cycloalkyl;

R² is phenyl, optionally substituted with 1 to 5 substituents independently selected from the group comprising OH, C1-C6 -alkyl, halogen, nitro, cyano, SH, SR⁴, trihalo-C1-C6-alkyl, C1-C6 -alkoxy and phenyl, wherein R⁴ is C1-C6 alkyl;

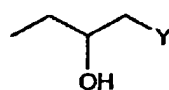
R³ is phenyl substituted with OR⁵ wherein R⁵ has the formula (II) (III) or (IV)



(II)



(III)



(IV)

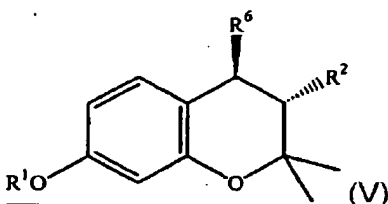
wherein Y is chosen from NHR⁴, NR⁴₂, NHCOR⁴, NHSO₂R⁴, CONHR⁴, CONR⁴₂, COOR⁴, SO₂R⁴, SOR⁴, SONHR⁴, SONR⁴₂, a C3-C7 heterocyclic ring, saturated or unsaturated, containing one or two heteroatoms independently selected from the group consisting of O, S and N, optionally being substituted with 1 to 3 substituents independently selected from the group comprising H, OH, halogen, nitro, cyano, SH, SR⁴, trihalo-C1-C6-alkyl, C1-C6-alkyl and C1-C6 -alkoxy, preferably including NHR⁴, NR⁴₂, or a nitrogen heterocycle, wherein R⁴ is as defined above;

said process comprising steps of:

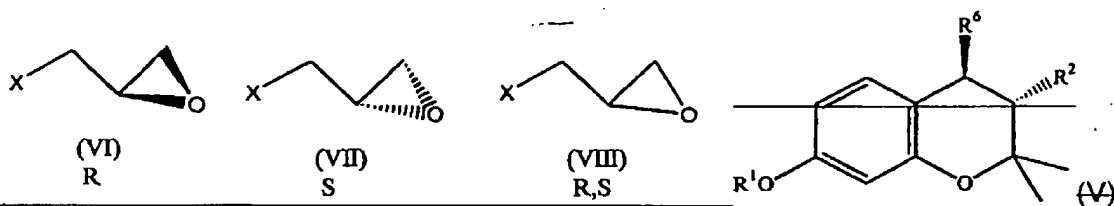
I. reacting a compound of formula V

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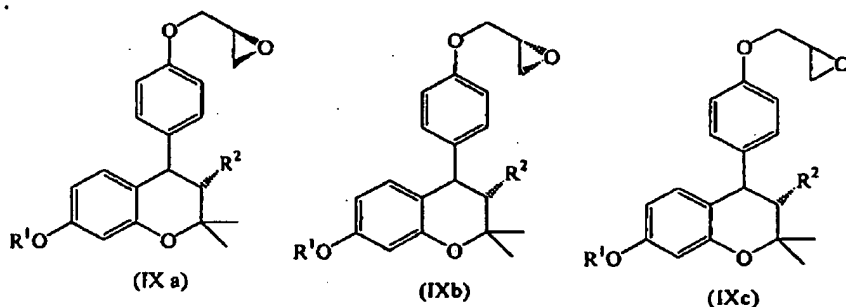
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in which substituents R^2 and R^6 are arranged in the (3R,4R) configuration: wherein R^1 and R^2 are as defined in formula 1 R^1 and R^2 are as defined in formula 1 is H or C1-C6 alkyl; C3-C7 cycloalkyl; R^2 is phenyl, optionally substituted with 1 to 5 substituents independently selected from the group comprising OH, C1-C6 alkyl, halogen, nitro, cyano, SH, SR^4 , trihalo C1-C6 alkyl, C1-C6 alkoxy and phenyl, wherein R^4 is C1-C6 alkyl; and R^6 is phenyl substituted with a hydroxy substituents at C2, C3 or C4, with a compound of formula VI, VII, VIII, neat or in an aprotic solvent which includes dimethylsulphoxide, dimethylformamide in the presence of a base including K_2CO_3 at temperature ranging between 50 to 120°C,

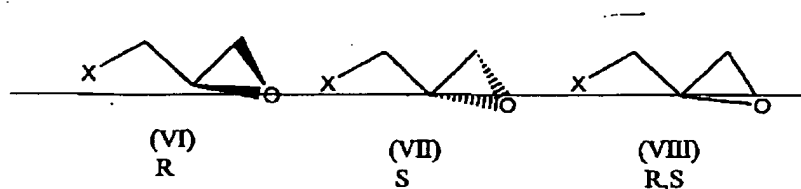


II. obtaining compounds of structure IX (a-c) wherein R^1 and R^2 are as defined in formula 1,

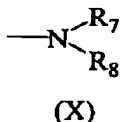


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III. reacting compound of formula IX a-c with a nucleophile including an amine of formula X :

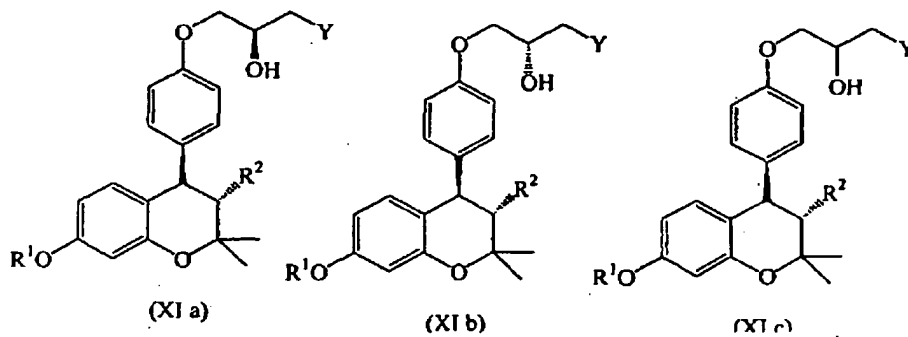


wherein R^7 and R^8 are individually hydrogen, C1-C6-alkyl which includes straight chain as well as branched alkyl groups including methyl, ethyl, propyl, isopropyl, butyl, isobutyl C1-C6-cycloalkyl which includes cyclopropane, cyclobutane, cyclopentane, cyclohexane or form a C3-C7 heterocyclic ring, saturated or unsaturated containing one or two heteroatoms independently selected from the group comprising O, S and N, optionally being substituted with 1,2,3 substituents independently selected from the group comprising H, OH, halogen, nitro, cyano, SH, SR^4 , trihalo-C1-C6-alkyl, C1-C6-alkyl and C1-C6-alkoxy, wherein R^4 is defined above, either neat or in the presence of organic solvent including benzene, dimethylsulphoxide, dimethylformamide, and

IV. obtaining compounds of formula XI a-c, optionally converting the amino derivative into their corresponding salts including HCL, fumarate, citrate by treating the free base with the corresponding acid,

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wherein Y, R¹ and R² are as defined above.

Claims 14-32 (Canceled)